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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,841	01/15/2004	Michael Wayne Graham	0687/74768-AA/JPW/GJG/JRM	8757

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EXAMINER	
WHITEMAN, BRIAN A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,841	GRAHAM ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *172,176-179,181,184-188,190-193,195,199,200,202-205,207,211 and 215-244* is/are rejected.

7)☒ Claim(s) *182,183,196,197,208, 209,212-214* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/09,10/2/09,9/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 172,176-179,181-188,190,193,195-197,199,200,202-205,207-209 and 211-244.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 9/28/09 has been entered.

Election/Restrictions

Upon further consideration, the election of species mailed on 11/29/06 is withdrawn and the non-elected species are rejoined and examined with the elected species.

Information Disclosure Statement

The plasmid map in the information disclosure statement (IDS) filed on 9/28/09 and the Third party observation in the IDS filed on 10/2/09 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because there is no date listed for the map or observation. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information

disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 215-244 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention broadly reads on targeting a nucleotide sequence comprising about 20 nucleotides of a genus of visually-detectable gene. On page 15, lines 15-26, the specification recites:

> Preferred structural gene components of the synthetic gene of the invention comprise at least\about 20-30 nucleotides in length derived from a viral DNA polymerase, viral RNA polymerase, viral coat protein or visually-detectable gene, more particularly an RNA polymerase gene derived from a virus selected from the list comprising BEV, Sindbis alphavirus, HIV-I, bovine herpes virus and HSV1 or a visually-detectable gene which is

> involved in determining pigmentation, cell death or other external phenotype on a cell, tissue, organ or organism, amongst others.
>
> In a particularly preferred embodiment, the structural gene component of the synthetic gene comprises at least about 20-30 nucleotides in length derived from the BEV RNA-dependent RNA polymerase gene or the murine tyrosinase gene or the Escherichia coli lac repressor gene lacI or a complementary sequence thereto.

The specification does not define what is considered to be a visually-detectable gene. The specification discloses determining pigmentation (e.g., murine tyrosinase gene) or E. coli lac repressor lacI. The specification further describes expression constructs that contain full-length sequences from tyrosinase, GFP, and LacI gene and fragments 100-200 bases in length of tyrosinase. However, with respect to the limitation "visually detectable gene which is involved in determining pigmentation, cell death or other external phenotypes in a cell, tissue organ or organism," the specification does not provide a structure for what genes are embraced by these species. In view of the absence of a definition for the term in the specification and the different functions embraced by possibly each species there is a variation between species embraced by the genus recited in the claims. The prior art of record does not provide representative samples of the genus of sequences comprising about 20 nucleotides from a visually detectable gene. At the time of filing, neither the specification nor the art of record provide support for the skilled artisan to envision what genes are embraced by the claimed genus.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as

of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the detailed structure of the encompassed genus of compounds that are structural gene sequences to a region of a target gene comprising about 20 nucleotides of a visually detectable gene, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, while the specification provides adequate description of constructs containing full-length sequences of tyrosinase, GFP and LacI genes, the full breadth of the many genes, known or unknown, and the many compounds that target gene comprising about 20 nucleotides of a visually detectable gene and reduce expression of the target gene that are encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

With respect to the term “stuffer fragment”, the instant specification defines the term (see page 19, line 14 to page 20, line 14).

Claims 172, 176, 180, 181, 184, 185, 187, 188, 190, 195, 199, 200, 202, 207, 211, 214-219, 222, 223, 225-230, 233-238, and 241 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al (US 6,506,559, cited on a PTO-1449) taken with Cowsert et al. (US 5,580,767, of record).

Fire teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising dsRNA comprising a sense strand and an antisense strand of the target gene (columns 4 and 9). The sequence can comprise one or more strands of the nucleotide sequence (column 4). The dsRNA may be formed by a single self-complementary RNA strand or two complementary RNA strands (column 7). A single self-complementary strand would indicate that the vector comprising nucleotides sequences would read on a stuffer between the sequences. In such a molecule having several nucleotide sequences, an arbitrary number of nucleotides associated with the inherent hairpin region of the strand can be arbitrarily considered to be a stuffer fragment that links 25 complementary base pair. This construct could have stuffer regions of one or more strands of the nucleotide sequence containing nucleotide bases on the arbitrary designation of what is, and what is not, the stuffer sequence. The construct comprises a regulatory region including polyadenylation (columns 8-9). The nucleotide sequence may be at least 25 or 50 bases (column 8). The vector can be introduced into a cancerous cell, including cancer cells find in humans (column 9-10). A viral vector can be used as the vector (column 9). Fire teaches using phagemid clones to produce the RNA (column 18). One of ordinary skill in the art understands that phagemid clones can be used for double stranded replication. The cell can comprise a

target gene at risk from a pathogen or can be from several different types of animals (columns 4, 8, and 10). The structural gene can be less than 2.0 kilobases (table 1 and Figure 1). However, Fire does not specifically teach targeting RNA polymerase of a viral gene.

However, at the time the invention was made, Cowsert teaches antisense oligonucleotides for inhibiting RNA polymerase (column 3).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising a construct comprising a structural gene encoding RNA polymerase of a virus. One of ordinary skill in the art would have been motivated to combine the teaching to improve and study the efficiency of inhibiting the virus.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising a construct comprising a structural gene encoding RNA polymerase of a lentivirus. One of ordinary skill in the art would have been motivated to combine the teaching to improve and study the efficiency of inhibiting the virus.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising a construct comprising a structural gene encoding RNA polymerase of an immunodeficiency virus. One of

ordinary skill in the art would have been motivated to combine the teaching to improve and study the efficiency of inhibiting the virus.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising a construct comprising a structural gene encoding RNA polymerase of a virus, wherein the gene is in an exon. One of ordinary skill in the art would have been motivated to combine the teaching to improve and study the efficiency of inhibiting the virus by targeting the exon.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising a construct comprising a structural gene encoding RNA polymerase of a virus, wherein the construct is no more than 0.5-2.0 kilobases. One of ordinary skill in the art would have been motivated to combine the teaching to improve and study the efficiency of inhibiting the virus. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising a construct comprising a structural gene encoding RNA polymerase of a virus, wherein the construct has a stuffer fragment of 10-50 nucleotides in length. One of ordinary skill in the art would have been

motivated to combine the teaching to improve and study the efficiency of inhibiting the virus by targeting multiple regions of the virus. In such a construct, an arbitrary number of nucleotides associated with the inherent hairpin region of the RNA strand can be arbitrarily considered to be a stuffer fragment that links 25 complementary base pair. This molecule could have stuffer regions of one or more strands of the nucleotide sequence containing nucleotide bases on the arbitrary designation of what is, and what is not, the stuffer sequence. See In re Aller, Id.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert, namely to produce an isolated mammalian cell comprising liposome or viral particle comprising a construct comprising a structural gene encoding RNA polymerase of a virus. One of ordinary skill in the art would have been motivated to combine the teaching to improve and study the efficiency of inhibiting the virus and to successfully deliver the construct to a cell of interest.

In view of the teaching of Fire (columns 8-9) and Cowsert (column 3), one of ordinary skill in the art would have had a reasonable expectation of success of producing the mammalian cell comprising the dsRNA construct. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 12/21/09 and 9/28/09 have been fully considered but they are not persuasive.

With respect to applicant's argument filed on 12/21/09 that the amendment to comprising about 20 consecutive nucleotides or about 20 consecutive nucleotides or only about 20 consecutive nucleotides does not read on the teaching of at least 25 nucleotides taught by Fire and applicants disavow a construction of the range of "about 20" base pairs recited in the amended claims herein which would read on 25 base pairs at the upper end of the range and an analogous construction at the lower end of the range and to avoid prior art (see Purdue Pharma. L. P. v Endo Pharma., Inc., 438, F. 3d, 1123, 1136 Fed. Cir. 2006), the argument is not found persuasive because the specification does not define the term 'about'. The specification provides a broader claimed invention 'comprises at least about 20-30 nucleotides in length…' (page 10, lines 15-26) and does not indicate that consisting of about 20 nucleotides that is less than 25 nucleotides is a critical element for practicing the claimed invention. See MPEP 2144.05 II. Thus, the limitations still reads on at least 25 nucleotides. Furthermore, "Prosecution disclaimer does not apply to an ambiguous disavowal." See N. Telecom Ltd. v. Samsung Elec. Co. 215 F.3d 1281, 1293-95 (Fed. Cir. 2000) (holding that prosecution disclaimer did not "support the judicial narrowing of a clear claims term" because the inventors' statements were amendable to multiple reasonable interpretations). "Occasionally specification explanations may lead one of ordinary skill to interpret a patent claim term more narrowly than its plain meaning suggests, but the importation of claim limitations from a few specification statements or figures into the

claims is not permissible, particularly if those specification extracts describe only embodiments of a broader claimed invention." See Computer Docking Station Corp v. Dell, Inc. 519 F.3d 1366 (Fed. Cir. 2008).

In response to applicant's argument that there was skepticism in the prior art about extrapolating the results observed in C. elegans to other organisms (see Wagner and Riggs, Nature 1998 and Riggs Declaration), the argument is not found persuasive because the Fire provisional contemplates using the dsRNA in mammalian cells, thus one of ordinary skill in the art would be motivated to try administering the dsRNA to mammalian cells. Fire taught that the introduction of dsRNA is at least 100-fold more effective than the injection of purified antisense RNA in inhibiting gene expression. Fire taught the use of viral vectors to deliver the dsRNA molecules in the cell. Furthermore, the present specification appears to only provide generic disclosure and no actual examples of inhibiting gene expression using the claimed construct in mammalian cells, which is similar to the teaching of Fire.

In response to applicant's argument that the preferred route of administering the dsRNA is direct administration and not viral vectors, the argument is not found persuasive because one of ordinary skill in the art would have been motivated to use a vector for long-term expression of the dsRNA or for controlled expression of the dsRNA. "A reference may be relied upon for all that it would reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments." See Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert denied, 493 U.S. 975 (1989). Also see In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Furthermore, applicant admitted that the routine procedure for transfecting animal cells with nucleic acid molecules to produce transiently or stably transfected animal cells were available prior to the filing date of the present invention (see pages 10 and 11 of the response filed on 11/14/00 in the application 09/100,812.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case because even though Cowsert is not directed to using a nucleic acid inhibitor for RNA interference, Fire taken with Cowsert provide motivation for one of ordinary skill in the art to use a construct for expressing each strand of the nucleotide sequence. Citing KSR, the Board stated that "when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." See Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007).

With respect to the argument that the intended use of the claimed product is not disclosed in the prior art, the intended use does not carry patentable weight over a product taught in the prior art teaching or making obvious the claimed product.

In response to applicant's argument that the possibility of polyadenylation made it impossible to predict whether the claimed invention would successfully cause RNA

interference, the argument is not found persuasive because the present specification appears to only provide generic disclosure and no actual examples of inhibiting gene expression using the claimed construct in mammalian cells, which is similar to the teaching of Fire. The instant claims do not require a polyadenylation tail for the product. In addition, if this was a cause for concern in the prior art, there are several promoters used in the prior art that do not result in polyadenylation of the product.

In response to applicant's argument that substantial evidence of secondary consideration negates the alleged obviousness of the claimed invention because the skepticism of experts at the time (see Tuschl Nature Biotechnology, 2002 and Yu et al. (PNAS, 2000).

The argument is not found persuasive both references lack the required nexus to the present claims. As further explained below, the present claims are not specific to siRNA having 21 nucleotides for regulating gene expression. Thus, the evidence of secondary consideration submitted by applicant is not considered to outweigh the evidence of obviousness.

The Declaration under 37 CFR 1.132 filed on 9/28/09 is sufficient to overcome the 103(a) rejection of claims 172 based upon Fire taken with Cowsert.

Dr. Riggs has proposed several possible challenges the dsRNA may face in the nucleus. NOTE: the present specification does not address these concerns by one skilled in the art (Dr. Riggs). Thus, these issues could also be directed to the instant claims.

The claimed invention only discusses a sequence or length in terms of DNA contained in vectors, never any length of RNA produced by such vectors; that even if the sequence contain only 20-30 nucleotides, this does not necessarily result in RNA transcripts having this same length. See Appeal Brief filed on application 10/805,804.

In response to Dr. Riggs statement that Cowsert is not a reference from the gene silencing art, but teaches an example of antisense oligonucleotides to inhibit the function of influenza virus RNA, the statement is not persuasive. First as mentioned by Dr. Riggs, using dsRNA to inhibit a target gene in a cell has never been reported before, thus there would be no prior art on the topic other than the teaching of Fire. It is acknowledged that Cowsert reference is not directed to gene silencing, however, Cowsert teaches a nucleic acid inhibitor and Fire teaches that dsRNA is more potent than antisense oligonucleotides for inhibiting gene expression. Thus, one of ordinary skill would have been motivated to try using the dsRNA targeting to influenza virus RNA to determine if dsRNA is more effective at inhibiting gene expression compared to antisense oligonucleotides. See KSR vs. Teleflex, Id.

Dr. Riggs states that it is impossible to predict how the effects would be affected by changes made to the experimental system reported by Fire et al.

First, obviousness requires a reasonable expectation of success, but not absolute certainty. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

As admitted by applicants (see pages 10 and 11 of the response filed on 11/14/00 in the application 09/100,812), it was routine for one of ordinary skill in the art

at the time of filing to transfect animal cells with nucleic acid sequences to produce transiently or stably transfected animal cell. Furthermore, Fire discloses ex vivo or in vivo introduction of dsRNA into the cell of an organism for inhibiting gene expression. While it is agreed that at the time of filing that Fire did not know the mechanism (RNAi) that resulted in inhibiting expression of a target gene using dsRNA, the instant specification was also unaware of the mechanism involved in inhibiting expression of a target gene using dsRNA encoded by a genetic construct. In view of the prior art of record, one of ordinary skill in the art would have been motivated to make and use a vector comprising the dsRNA for long-term or controlled expression of the dsRNA in mammalian cells compared to direct administration of the dsRNA to the cells.

Dr. Riggs states that shortest RNA with which Fire et al. observed was 299 base pairs longs and even though Fire discloses lengths from 25 to 400 base pairs corresponding to the target gene, the mechanism was unknown and one of ordinary skill in the art would not know the size requirement nor predict the consequence of decreasing the length of the RNA duplex.

The statement is not found persuasive because Fire teaches using lengths of RNA from 25 to 400 base pairs and the prior art (Manche, of record) teaches that dsRNA longer than 30 base pairs induces a cellular immune response, thus providing motivation to try sequences below 30 base pairs, e.g., 25 base pairs and making 25 base pairs is cheaper than making 299 base pairs. Furthermore, the as-filed specification does not teach the mechanism that was supposedly lacking from Fire et al. Other than the instant specification contemplating and claiming the genetic constructs

having at least 20-30 nucleotides of specific target genes or making the constructs in the working example, the teaching of the present application does not provide the mechanism of RNA interference and correlate what size operates in RNA interference that is lacking from Fire.

Dr. Riggs states that except for the delivery of dsRNA to the gonads and the body cavity of C. elegans, all other delivery methods were untested and unpredictable.

The statement is not found persuasive because the prior art of record provides motivation and a reasonable expectation of success for administering a viral vector comprising the dsRNA to a mammalian cells. Obviousness requires a reasonable expectation of success, but not absolute certainty. In re O'Farrell, Id. Furthermore, the use of routine procedures for transfecting animal cells with nucleic acid molecules to produce transiently or stably transfected animal cells, taught by Fire taken with Cowsert would result in transcription of the sense and antisense strands in close proximity to each other thus ensuring favorable binding of the resulting duplex. Furthermore, Fire specifically taught “a viral vector packages into a viral particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector” (Fire provisional, page 12).

Dr. Riggs states that double-stranded RNA may not form in the nucleus and it would have been difficult to predict if the independent strands could form RNA duplexes in the nucleus to mediate gene silencing.

The statement is not found persuasive because Fire taught self-complementary can be used in the method and specifically taught “a viral vector packages into a viral

particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector" (Fire provisional, page 12). Also see In re O'Farrell, Id.

Dr. Riggs Declaration refers to Okano (1991, Exhibit D) in support of the argument that dsRNA may get trapped in the nucleus and it was possible that the dsRNA produced in the nucleus could suffer the same fate.

The statement is not found persuasive because Fire taught that the dsRNA-mediated inhibition showed an ability to cross cellular boundaries (see Fire provisional, page 20). The intracellular localization of the dsRNA transcribed by the DNA construct is determined by the type of vector and the design of the vector. The instant claims are not limited to transportation of the dsRNA transcribed by the DNA construct to the cytoplasm.

Dr. Riggs Declaration refers to Kumar et al., (1998, Exhibit E) in support of the argument that dsRNA may get modified in the nucleus and it could not have been predicted whether the effect of inosines would have on the system reported by Fire et al.

The statement is not found persuasive because the reference is a post-filing reference and the information disclosed by Kumar appears not to be issue before the filing of Fire et al.

Dr. Riggs Declaration refers to Wu et al., (JBC, 1998, Exhibit F) in support of the argument that dsRNA may get degraded in the nucleus and it could not have been predicted whether duplex structures would be degraded in the nucleus, thus

compromising the double-stranded RNA and the ability to specifically silence gene as reported by Fire et al.

The Wu publication is after the filing date of Fire and appears to be unknown before the filing date of Fire et al. Thus, one of ordinary skill in the art would have been aware of the issue.

Dr. Riggs declares that polyadenylation at the 3' end of RNA may interfere with RNA interference (see Exhibits G, H and I).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inclusion of a poly-A tail) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore if polyadenylation at the 3' end of the RNA was a concerned by the skilled artisan, there are several well known promoters (e.g., bacteriophage T7 promoter) were polyadenylation does not occur in transcripts generated from it.

Dr. Riggs states that heterogenous nuclear ribonucleoproteins may affect double-stranded RNA formation Lodish (exhibit G, 1999).

The statement is not found persuasive because the Lodish's reference is post-filing reference which would have been unknown at the Fire was filed.

Dr. Riggs states that claimed invention teaches the use of DNA constructs that would produce double-stranded RNA having a duplex region that has only 20-30 base pairs.

The statement is not found persuasive because the claimed invention only discusses a sequence or length in terms of DNA contained in vectors, never any length of RNA produced by such vectors; that even if the sequence contain only 20-30 nucleotides, this does not necessarily result in RNA transcripts having this same length. See Appeal Brief filed on application 10/805,804.

Claims 172, 176-179, 181, 184-188, 190-193, 195, 199, 200, 202-205, 207, and 211 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, cited on an IDS) in view of Kool (US 5,514,546, cited on an IDS) and Cowsert et al. (US 5,580,767, of record).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The size of the self complementary region may vary, but may be so extensive as to involve every nucleotide of the oligonucleotide, i.e. it may be 8-50 nucleotides in length (see page 15, lines 3-6, 16-21, and 26-30). The resulting RNA may form a hairpin structure comprising a loop, see page 15, lines 12-16, and Fig. 1. The loop is considered to be a “stuffer” sequence.

Thus, Agrawal fairly taught a double stranded RNA comprising a target hybridizing region of 8-50 ribonucleotides, a loop, and a self-complementary region of 8-50 nucleotides. In addition, Agrawal teaches nucleotide and non-nucleotide linkers that would connect the two nucleotide sequences (pages 14-17). The target gene may be a viral gene. Disclosed viruses include human immunodeficiency virus, Yellow Fever virus (a single strand (+) RNA virus), and Herpes simplex virus (a double stranded DNA virus). See paragraph bridging pages 10 and 11. Absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to vary the length of the unpaired loop sequence of the self-stabilizing RNA of Agrawal in order to optimize hybridization of the complementary section of the oligonucleotides, thereby providing increased stability against nucleolytic attack. However, Agrawal does not explicitly teach vectors encoding the antisense oligonucleotides, oligonucleotides targeting a coding region, or liposome-containing compositions.

However, at the time the invention was made, Kool taught delivery of stem-loop oligonucleotides by expression vector or by direct application of the oligonucleotides. See abstract; Fig. 1; column 3, lines 16-19 and lines 58-62; column 4, lines 6-17; and column 14, line 39. Kool also disclosed antisense inhibition by targeting coding regions. See column 7, lines 43-46. Kool also disclosed delivery of expression vectors by viral- or liposome-mediated transfection. See column 15, lines 36-45; column 16, lines 43-47; paragraph bridging columns 24 and 25; and column 29, lines 32 and 33.

In addition, at the time the invention was made, Cowsert teaches antisense for inhibiting RNA polymerase (column 3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the oligonucleotides of Agrawal by use of the expression vector of Kool and inhibiting viral RNA polymerase taught by Cowsert. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Thus the delivery techniques of Kool, i.e. direct application of oligonucleotides, and transfection of oligonucleotide expression vectors, are considered to be exchangeable equivalents. Alternatively, the method of delivering the oligonucleotides can be viewed as a matter of design choice. Moreover, one would have been motivated to use the expression vector of Kool in order to obtain continuous synthesis and action of oligonucleotides for the amount of time that the vector was present in the cell. Generally, expression vectors can be made with selectable markers that allow their maintenance in a cell for a longer time than the expected lifetime of an oligonucleotide. Thus, one of ordinary skill in the art could reasonably expect to obtain antisense inhibition for a longer period of time with the expression vector of Kool.

It would have been similarly obvious to target coding regions of target genes, and to deliver the vectors by viral or liposomal means as suggested by Kool. See KSR v. Teleflex, Id.,

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/28/09 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prosecution history of US application 09/215,257, which later issued as US 6,506,559 (see public PAIR) indicates that even though Agrawal does not teach using dsRNA for RNA interference, Agrawal was cited as prior art against the claims of Fire until Fire amended claims to read on two separate RNA strands. Thus, this indicates that the product of Agrawal is considered prior art against the claimed invention which reads on the claims and teaching of Fire.

The Declaration under 37 CFR 1.132 filed on 9/28/09 is sufficient to overcome the 103(a) rejection of claims 172 based upon Agrawal taken with Kool and Cowsert.

Dr. Riggs states that since Agrawal is directed to antisense technology, Agrawal does not offer any teaching that one of ordinary skill in the art cold have applied to predictably modify the teachings of Fire to produce applicant's invention.

The statement is not found persuasive because if Agrawal taught RNA interference then neither RNA interference nor the teaching of either Fire or the instant application would be considered novel as indicated by Dr. Riggs. Agrawal is cited because Agrawal teaches a product the meets the structural and functional limitations of the claimed product. In response to applicant's argument that the references fail to

show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., RNA interference) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Dr. Riggs declares that Kool is irrelevant to the instant invention because Kool is directed to stem-loop oligonucleotides.

The statement is not found persuasive because if Kool taught RNA interference then neither RNA interference nor the teaching of either Fire or the instant application would be considered novel as indicated by Dr. Riggs. Kool is cited because Kool in combination with Agrawal provide motivation and a reasonable expectation of success for using a promoter to express the product taught by Agrawal. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., RNA interference) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 172 , 177-179, 188, 191-193, 200, and 203-205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire taken with Cowsert as applied to claims 172, 176, 180, 181, 184, 185, 187, 188, 190, 195, 199, 200, 202, 207, 211, 214-219, 222, 223, 225-230, 233-238, and 241 above, and further in view of Agrawal.

Fire taken with Cowsert do not specially teach targeting a region of HIV.

However, at the time the invention was made, Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The size of the self complementary region may vary, but may be so extensive as to involve every nucleotide of the oligonucleotide, i.e. it may be 8-50 nucleotides in length (see page 15, lines 3-6, 16-21, and 26-30). The resulting RNA may form a hairpin structure comprising a loop, see page 15, lines 12-16, and Fig. 1. The loop is considered to be a “stuffer” sequence. Thus, Agrawal fairly taught a double stranded RNA comprising a target hybridizing region of 8-50 ribonucleotides, a loop, and a self-complementary region of 8-50 nucleotides. In addition, Agrawal teaches nucleotide and non-nucleotide linkers that would connect the two nucleotide sequences (pages 14-17). The target gene may be a viral gene. Disclosed viruses include human immunodeficiency virus, Yellow Fever virus (a single strand (+) RNA virus), and Herpes simplex virus (a double stranded DNA virus). See paragraph bridging pages 10 and 11.

Absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to vary the length of the unpaired loop sequence of the self-stabilizing RNA of Agrawal in order to optimize hybridization of the complementary section of the oligonucleotides, thereby providing increased stability against nucleolytic attack. .

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert in further view of Agrawal et al., namely to produce a vector comprising one promoter operably linked to a nucleotide sequence comprising the sense strand and another promoter operably linked to a nucleotide encoding comprising the antisense strand, wherein the antisense strand targets region of a HIV gene. One of ordinary skill in the art would have been motivated to combine the teaching to study the efficiency of inhibition of a target HIV gene.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments and Declaration filed 9/28/09 have been fully considered but they are not persuasive for the reasons set forth above.

Claims 172, 186, 215, and 224 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire taken with Cowsert as applied to claims 172, 176, 180, 181, 184, 185, 187, 188, 190, 195, 199, 200, 202, 207, 211, 214-219, 222, 223, 225-230, 233-238, and 241 above, and further in view of Kool (of record).

Fire and Cowsert do not specifically teach using a liposome to deliver the construct.

However, at the time the invention was made, Kool teaches using a liposome to deliver a nucleic acid to a cell.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Cowsert in further view of Kool, namely to produce a liposome comprising the construct. One of ordinary skill in the art would have been motivated to combine the teaching to deliver the construct to cells. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments and Declaration filed 9/28/09 have been fully considered but they are not persuasive for the reasons set forth above.

Response to Arguments

Applicant's arguments, see page 14, filed 12/21/09, with respect to obviousness double patenting rejection have been fully considered and are persuasive because of the terminal disclaimer. The rejection of claim 172 has been withdrawn.

Conclusion

Claims 182, 183, 196, 197, 208, 209, and 212-214 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635